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EXAMINER

WOOLWINE, SAMUEL C

ART UNIT	PAPER NUMBER
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1637

DATE MAILED: 02/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b>		<b>Applicant(s)</b>	
	10/056,229		REMACLE ET AL.	
	<b>Examiner</b>		<b>Art Unit</b>	
	Samuel Woolwine		1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 20 July 2005.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-8, 11-18, 20-23, 25-27, 29-36, 38-40, 44-61, 81 and 83-94 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-8, 11-18, 20-23, 25-27, 29-36, 38-40, 44-61, 81 and 83-94 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                        | 4) <input type="checkbox"/> Interview Summary (PTO-413)                     |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)               | Paper No(s)/Mail Date. _____  |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date <u>9/2/05, 7/14/05, 10/12/05</u>   | 6) <input type="checkbox"/> Other: _____                                    |

**DETAILED ACTION**

This application has been re-assigned to Examiner Samuel Woolwine, whose contact information appears on the last page of this Office Action. Any rejection not reiterated in this Office Action has been withdrawn as no longer applicable.

***Continued Examination Under 37 CFR 1.114***

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 20, 2005, has been entered.

***Status***

Claims 1-8, 11-18, 20-23, 25-27, 29-36, 38-40, 44-61, 81, and 83-94 are pending. Claims 9, 10, 19, 24, 28, 37, 41-43, 62-80, and 82 are cancelled.

***Response to Arguments***

Applicant's arguments with respect to claims 1-46, 48-61, and 80-94, rejected under 35 U.S.C. 103(a) in the Office Action entered 01/02/2004, have been considered but are moot in view of the new ground(s) of rejection.

***Claim Interpretation***

With regard to claim limitations regarding the term “homologous”, Applicant explicitly defines “homologous genetic sequences” in paragraph [0037] of the specification:

“The terms “homologous genetic sequences” mean amino acid or nucleotide sequences having a percentage of amino acids or nucleotides identical at corresponding positions which is higher than in purely random alignments. They are considered as homologous when they show a minimum of homology (or sequence identity) defined as the percentage of identical nucleotides or amino acids found at each position compared to a total of nucleotides or amino acids, after the sequences have been optimally aligned taking into account additions or deletions (like gaps) in one of the two sequences to be compared. Genes coding for a given protein but present in genetically different sources like different organisms are usually homologous. Also in a given organism, genes coding for proteins or enzymes of the same family (Interleukins, cytochrome b, p. 450). The degree of homology (or sequence identity) can vary a lot as homologous sequences may be homologous only in one part, a few parts or portions or all along their sequences.” (emphasis added)

Applicant has not disclosed a particular percentage or percentage range of sequence identity that defines “homologous”. Nor has Applicant defined what constitutes “a minimum of homology” or what constitutes “optimally aligned”. Applicant defines homologous sequences as having a percentage identity “at corresponding positions which is higher than in purely random alignments”, but has not disclosed what percentage of sequence identity is found in “purely random alignments”. Further, Applicant states that “[t]he degree of homology...can vary a lot”. Consequently, claim limitations regarding the term “homologous” are subject to a broad interpretation.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

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The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 11, 36 and 81 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

With regard to claim 11, it is not clear whether the capture nucleotide sequences comprise a sequence which is between about 100 and 600 bases in length, or whether the target comprises a sequence which is between about 100 and 600 bases in length.

Claim 36 recites the limitation "using a member selected from the group consisting of a consensus primer and a stopper sequence". The specification was searched for the term "stopper sequence" and was not found. It is unclear what a "stopper sequence" is.

Claim 81, depending from claim 1, recites "said...sequence of between about 15 and about 40 bases". There is insufficient antecedent basis in either claim 81 or 1 for this limitation. It appears this limitation refers to an earlier version of claim 1 and was not amended concordantly.

### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

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(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-8, 11-14, 18, 22, 23, 25-27, 29-34, 39-40, 44-45, 55-57, 59-61, 81, 83 and 87 are rejected under 35 U.S.C. 102(b) as being anticipated by Guschin et al (1997) as evidenced by Yershov et al (1996), Ershov et al (USPN 5,770,721, issued 6/23/1998), Kulisch (US 2006/0003308 A1), and Whitlock (US 2005/0106126 A1).

With regard to claim 1, Guschin teaches a method comprising:

amplifying or copying at least one of said homologous nucleotide sequences into target homologous nucleotide sequences using primer pairs which are capable of amplifying or copying at least four of said target homologous nucleotide sequences from other organisms See page 2398, first sentence under *Cloning of 16S rDNA and in vitro production of RNA transcripts*. Guschin uses two primers, S-D-Bact-0011-a-S-17 and S-D-Bact-1492-a-A-21, to amplify 16S rDNA sequences from DNA extracted from five different species of bacteria. See also page 2401, column 2, first three sentences of fourth paragraph).

contacting said target homologous nucleotide sequences with single-stranded different capture nucleotide sequences, at least two of said single-stranded capture nucleotide sequences being specific for at least two of said target homologous nucleotide sequences See table 1. The array contains at least 9 capture nucleotide sequences including sequences specific for

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*Nitrobacter*, *Nitrosomonas*, and *Nitrosovibrio*-like rDNA. See also page 2401, column 2, first three sentences of fourth paragraph

said single-stranded capture nucleotide sequences being covalently bound in an array to an insoluble solid support via a spacer which is at least 6.8nm in length See page 2398, column 2, *Microchip fabrication*.

Oligonucleotides were coupled to polyacrylamide gel pads that were 20µm thick. Guschin teaches manufacturing the microarray as described in reference 35. Specifically, according to reference 35, the glass substrate was treated with Bind-Silane (Yershov et al, 1996, page 4914 column 2, *Microchip Manufacturing*, 1<sup>st</sup> sentence). Bind-Silane allows for covalent bond formation between the glass and the polyacrylamide gel slabs, as evidenced by Ershov et al (USPN 5,770,721) column 3, lines 45-50: "To provide better adhesion for the polyacrylamide gel so that covalent bonds can be formed between the glass and the gel, a layer of Bind-Silane is put down on the substrate". Therefore, the method taught by Guschin calls for covalent attachment of the polyacrylamide gel pads (i.e. the "spacer") to a glass substrate (i.e. the solid support) followed by the covalent attachment of the oligonucleotide probes to the gel pads.

said array comprising at least four different bound single-stranded capture nucleotide sequences/cm<sup>2</sup> of solid support surface See page 2398, column 2, *Microchip fabrication*. The gel pads were either 60 by 60 by 20 µm or 100 by 100 by 20 µm and were spaced 120 or 200 µm apart, respectively. Even with the larger sized gel pads, this would equate to 1 gel pad (i.e. one specific single-stranded capture nucleotide sequence) per 300 µm. Since 1 cm = 10,000 µm, up

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to 33 by 33 (i.e. 1089) single-stranded capture nucleotide sequences per cm<sup>2</sup> of solid support surface would be attained.

and wherein each of said single-stranded capture nucleotide sequences comprises a nucleotide sequence of about 5 to about 60 bases wherein said nucleotide sequence of about 5 to about 60 bases is able to specifically bind to one of the target homologous nucleotide sequences without binding to said at least four other homologous nucleotide sequences See table 1, page 2398. The probes are all within the size range of about 5 to about 60 bases. See also figure 1. Note that while figure 1 appears to show some cross-hybridization of the *Nitrosovibrio* target nucleic acid to the *Nitrosomonas* probe, Guschin teaches on page 2399, column 2, lines 8-14:

"In a like manner, the 16S rRNA of *Nitrosovibrio tenuis* hybridized to *Nitrosomonas* (Nsm156) at 10°C but was reduced to near background (compared to NonBac338) following the 40°C wash. A more complete correction for differences in stabilities of duplexes can be carried out by measuring the equilibrium or nonequilibrium melting curves for all microchip elements"

wherein said array also contains consensus capture nucleotide sequences for a common detection of said target homologous nucleotide sequences See tables 1 and 2 and figure 1. The array contains at least 9 capture nucleotide sequences including consensus capture nucleotide sequences able to bind target homologous sequences from all bacteria (probe S-D-Bact-0338-a-A-18) and "almost all life" (probe S-\*-Univ-1390-a-A-18).

said consensus capture nucleotide sequences having a length specific of the target comprising between about 10 and about 1000 bases The probes S-D-



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Bact-0338-a-A-18 and S\*-Univ-1390-a-A-18 are each in the range of about 10 to about 1000 bases. See table 1.

and detecting specific hybridization of the target homologous nucleotide sequence to said single-stranded capture nucleotide sequences See page 2398, column 2, *Hybridization and image analysis*. See also figure 1.

wherein said single-stranded capture nucleotide sequence is bound to the insoluble solid support at a specific location upon the array See table 2 and figure 1.

and wherein the binding between said target homologous nucleotide sequence and its corresponding single-stranded capture nucleotide sequence forms a signal at the expected location See figure 1.

the detection of said signal allowing a discrimination of the target homologous nucleotide sequence being specific of said organism from other organisms from the same or other groups, sub-groups of sub-sub-groups of said organisms See figure 1. Guschin also teaches on page 2397, column 2, last sentence of first full paragraph: "For example, the sequence diversity of SSU rRNAs recovered from different microbial populations of various abundances could be analyzed by a single hybridization to the microchip".

With regard to claims 2 and 3, the limitation wherein said biological organism is present in the sample among at least 2 [or 4] other organisms is a recitation of intended use. The method as taught by Guschin would accomplish this use. Guschin also teaches on page 2397, column 2, last sentence of first full paragraph: "For example, the sequence diversity of SSU rRNAs recovered from

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different microbial populations of various abundances could be analyzed by a single hybridization to the microchip”.

With regard to claim 4, see page 2398, *Cloning of 16S rDNA and in vitro production of RNA transcripts*, 1<sup>st</sup> sentence. Guschin teaches extracting DNA.

With regard to claim 5, see page 2398, column 2, *RNA and DNA labeling and fragmentation*. Guschin teaches labeling of the target nucleic acid sequences with fluorescein isothiocyanate, 6-carboxyfluorescein succinamide, or tetramethylrhodamine-hydrazide.

With regard to claim 6, see tables 1 and 2 and figure 1. Guschin teaches a method of detecting microorganisms. Guschin also teaches on page 2397, column 2, last sentence of first full paragraph: “For example, the sequence diversity of SSU rRNAs recovered from different microbial populations of various abundances could be analyzed by a single hybridization to the microchip”.

With regard to claim 7, see table 1, 2 and figure 1. Guschin teaches the detection of specific groups, sub-groups, and sub-sub-groups of organisms. For example, according to tables 1 and 2 and figure 1, binding between target homologous nucleotide sequences and corresponding consensus capture nucleotide sequences forms a signal at an expected location allowing the identification of a target nucleotide sequence specific of a group (table 1, probe S\*-Univ-1390-a-A-18, “almost all life”), sub-group (table 1, probe S-D-Bact-0338-a-A-18, eubacteria) and sub-sub-group (table 1, probe S-G-Nit-1000-b-A-15, genus *Nitrobacter*; probe S-G-Nsm-0156-a-A-19, genus *Nitrosomonas*; probe S\*-Nsv-04443-a-A-19, *Nitrosovibrio*-like genus).

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With regard to claim 8, see table 1, 2 and figure 1. Guschin teaches an array comprising a first category of capture nucleotide sequences being specific for individual target nucleotide sequences or their sub-groups (see table 1, probe S-G-Nit-1000-b-A-15, genus *Nitrobacter*, a sub-group of ammonia oxidizers) and a second category of capture nucleotide sequences being specific for all the nucleotide sequences of the group (see table 1, probe S-\*-Nso-0190-a-A-19, all ammonia oxidizers).

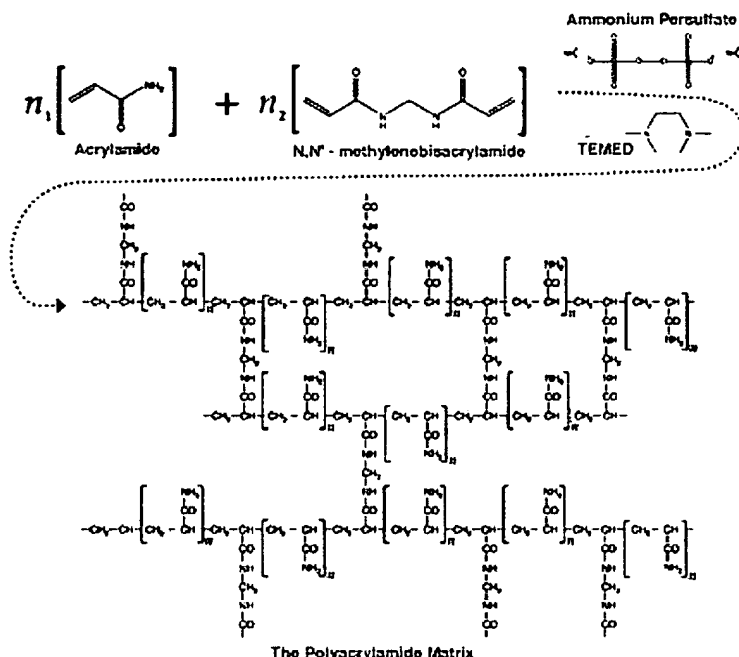
With regard to claim 11, the target homologous nucleotide sequences taught by Guschin are 16S ribosomal DNA or RNA. rDNA genes are approximately 1,500 base pairs (see page 2398, column 1, 2<sup>nd</sup> sentence under *Cloning of 16S rDNA and in vitro production of RNA transcripts*). Thus the target sequences taught by Guschin “comprise” sequences between about 100 and 600 bases in length.

With regard to claim 12, the target homologous nucleotide sequences taught by Guschin are 16S ribosomal DNA or RNA. Since all sequences encode structurally and functionally corresponding proteins in the respective organisms from which the sequences were derived, the sequences are homologous. The sequences are discriminated on the array upon corresponding polynucleotide sequences as taught by Guschin (see figure 1).

With regard to claims 13, 14, and 18, see page 2398, *Cloning of 16S rDNA and in vitro production of RNA transcripts*. Guschin uses two primers, S-D-Bact-0011-a-S-17 and S-D-Bact-1492-a-A-21, to amplify 16S rDNA sequences from DNA extracted from five different species of bacteria.

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With regard to claims 22 and 23, the “spacer” taught by Guschin is a polyacrylamide gel, which is branched:



With regard to claim 25, the capture nucleotide sequences in table 1 of Guscin range from 15 to 20 bases, which falls within the range of between about 20 and about 30 bases.

With regard to claims 26 and 27, Guscin teaches that 0.5 to 1 nl of oligonucleotide solution (at a concentration of 100 pmol/ml) was applied to each gel element (page 2398, column 2, *Microchip fabrication*). This equates to 0.05 to 0.1 fmol applied per gel element. For the 100 by 100  $\mu\text{m}$  gel elements, this amount of probe equates to 500-1000 fmol/ $\text{cm}^2$ .

With regard to claim 29, see table 1. The capture nucleotide sequences taught by Guscin are polynucleotides.

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With regard to claims 30-32, note that in table 1, the *Nitrosomonas* probe S-G-Nsm-0156-a-A-19 is 19 bases. Note also that according to figure 1, this probe contains 2 mismatches compared to the *Nitrosovibrio* 16S rRNA (figure 1A, right panel; see table 2 for location of probes on the array; probe S-G-Nsm-0156-a-A-19 is found at coordinate bII in figure 1). Thus, over the length of the 19 bases of the probe, the *Nitrosomonas* and *Nitrosovibrio* sequences are 17/19 or 89% homologous (identical).

With regard to claims 33 and 34, see page 2398, column 2, *RNA and DNA labeling and fragmentation*. Guschin teaches labeling of the target nucleic acid sequences with fluorescein isothiocyanate, 6-carboxyfluorescein succinamide, or tetramethylrhodamine-hydrazide. Guschin also teaches fragmenting the target sequences before hybridizing to the array.

With regard to claim 39, note that in table 1, the *Nitrosomonas* probe S-G-Nsm-0156-a-A-19 is 19 bases. Note also that according to figure 1, this probe contains 2 mismatches compared to the *Nitrosovibrio* 16S rRNA (figure 1A, right panel; see table 2 for location of probes on the array; probe S-G-Nsm-0156-a-A-19 is found at coordinate bII in figure 1).

With regard to claim 40, see table 1. The 9 single-stranded capture nucleotide sequences of the array differ from each other by one or more bases.

With regard to claim 44, Guschin teaches the method can be used to quantify. See page 2401, column 2, 3<sup>rd</sup> paragraph.

With regard to claim 45, the solid support taught by Guschin is glass; see page 2398, column 2, *Microchip fabrication*.

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With regard to claims 55-57, Guschin teaches identification of bacteria, falling within different genera. See page 2397, column 2, *Microbial strains*. *Nitrosomonas*, *Nitrosovibrio*, and *Nitrobacter* are all Gram-negative organisms as evidenced by US 2005/0106126 A1, paragraph [0068] and US 2006/0003308 A1, paragraph [0012].

With regard to claims 59-61 the limitations drawn to identification of the polymorphism of an organism, genotyping, and identification of a single nucleotide polymorphism are recitations of intended use. The method taught by Guschin would accomplish these functions. Also on page 2397, column 2, lines 2-6, Guschin teaches: "Yet, it [the method] has proven to be an excellent method for sequence analysis of mutations, gene polymorphisms, and other genetic changes. In this study, we further extend the utility of this format by demonstrating its application to studies in microbial ecology" (references omitted).

With regard to claim 81, notwithstanding the rejection of claim 81 under 35 U.S.C. 112, second paragraph, discussed above, see table 1, page 2398. The probes are all within the size range of about 15 to about 40 bases. See also figure 1. Note that while figure 1 appears to show some cross-hybridization of the *Nitrosovibrio* target nucleic acid to the *Nitrosomonas* probe, Guschin teaches on page 2399, column 2, lines 8-14:

"In a like manner, the 16S rRNA of *Nitrosovibrio tenuis* hybridized to *Nitrosomonas* (Nsm156) at 10°C but was reduced to near background (compared to NonBac338) following the 40°C wash. A more complete correction for differences in stabilities of duplexes can be carried out by measuring the equilibrium or nonequilibrium melting curves for all microchip elements"

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With regard to claim 83, note that in table 1, the *Nitrosomonas* probe S-G-Nsm-0156-a-A-19 is 19 bases. Note also that according to figure 1, this probe contains 2 mismatches compared to the *Nitrosovibrio* 16S rRNA (figure 1A, right panel; see table 2 for location of probes on the array; probe S-G-Nsm-0156-a-A-19 is found at coordinate bII in figure 1). Thus, over the length of the 19 bases of the probe, the *Nitrosomonas* and *Nitrosovibrio* sequences are 17/19 or 89% homologous (identical).

With regard to claim 87, see tables 1 and 2 and figure 1. The array contains at least 9 capture nucleotide sequences including consensus capture nucleotide sequences able to bind target homologous sequences from all bacteria (probe S-D-Bact-0338-a-A-18) and "almost all life" (probe S\*-Univ-1390-a-A-18).

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

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1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 15 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Guschin et al (1997) as applied to claims 1-8, 11-14, 18, 22, 23, 25-27, 29-34, 39-40, 44-45, 55-57, 59-61, 81, 83 and 87 above. Guschin teaches all of the limitations of claim 1 upon which claims 15 and 16 depend as discussed under the rejection of claim 1 under 35 U.S.C. 102 above. Guschin does not teach the detection of the amplified sequences, in the same chamber as amplification takes place, prior to hybridization. However, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention of the instant application was made to ensure the presence of amplified DNA prior to hybridizing it to the array. Since microarrays are expensive and hybridization



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and washing prior to detection are time-consuming, one would be motivated to use a system, such as real-time PCR, where amplification and detection of said amplification occur simultaneously, to save time and guarantee that microarrays are not wasted on samples in which amplification of target nucleic acids did not take place.

Claims 17 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Guschin as applied to claims 1-8, 11-14, 18, 22, 23, 25-27, 29-34, 39-40, 44-45, 55-57, 59-61, 81, 83 and 87 above, and further in view of Brown et al (USPN 5,807,522). Guschin teaches all of the limitations of claim 1, upon which claim 17 depends, as discussed in the rejection of claim 1 under 35 U.S.C. 102 above. Guschin does not teach a method of reverse transcribing mRNA into cDNA followed by amplification and hybridization.

Brown teaches the microarrays can be used in DNA hybridization assays, genotyping of organisms, identification of microorganisms, etc. (column 14, lines 35-42). Brown does not teach the use of a spacer or linker of 6.8 nm in length. Nor does Brown teach the use of primer pairs capable of amplifying or copying multiple homologous target sequences. However, Brown does teach mRNA can be reverse transcribed into cDNA and then amplified (see Example 2) prior to hybridization to a microarray.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention of the instant application was made to analyze homologous sequences by the method of Guschin using cDNA derived from mRNA after

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reverse transcription as taught by Brown. One would have been motivated to do so in order to use Guschin's array technology to study gene expression patterns of homologous nucleotide sequences.

Claims 20, 21 and 88 are rejected under 35 U.S.C. 103(a) as being unpatentable over Guschin as applied to claims 1-8, 11-14, 18, 22, 23, 25-27, 29-34, 39-40, 44-45, 55-57, 59-61, 81, 83 and 87 above, and further in view of Livak et al (USPN 5,723,591). Guschin teaches all of the limitations of claim 1 upon which claims 20, 21 and 88 depend as discussed under the rejection of claim 1 under 35 U.S.C. 102 above. Guschin does not teach using spacers composed of nucleotide sequences between about 15 and about 1000 bases.

Livak does not teach the use of a single pair of primers to amplify or copy multiple homologous target sequences. Livak *does* teach:

"A wide variety of linkers are known in the art which may be used to attach the oligonucleotide probe to the solid support. The linker may be formed of any compound which does not significantly interfere with the hybridization of the target sequence to the probe attached to the solid support. The linker may be formed of a homopolymeric oligonucleotide which can be readily added on to the linker by automated synthesis" (column 8, lines 1-7).

Livak does not teach using spacers composed of nucleotide sequences between about 15 and about 1000 bases.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention of the instant application was made to substitute the art-recognized functionally equivalent homopolymeric oligonucleotide spacer taught by Livak for the polyacrylamide spacer taught by Guschin for the detection of homologous sequences amplified with a single primer pair, as taught by Guschin,

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and to optimize the length of the oligonucleotide spacer. Regarding the substitution of equivalents known for the same purpose (in this case, to provide separation of an oligonucleotide probe from a solid support to which it is bound), MPEP 2144.06 states:

“In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant’s disclosure or the mere fact that the components at issue are functional or mechanical equivalents.”

Also from MPEP 2144.06:

“*Smith v. Hayashi*, 209 USPQ 754 (Bd. of Pat. Inter. 1980) (The mere fact that phthalocyanine and selenium function as equivalent photoconductors in the claimed environment was not sufficient to establish that one would have been obvious over the other. **However, there was evidence that both phthalocyanine and selenium were known photoconductors in the art of electrophotography.** “This, in our view, presents strong evidence of obviousness in substituting one for the other in an electrophotographic environment as a photoconductor.” 209 USPQ at 759.).

An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982).” (emphasis added)

In this instance, Guschin teaches the use of polyacrylamide to link oligonucleotides to a solid support, while Livak teaches using homopolymeric oligonucleotide for the same purpose. As in *Smith*, above, this provides evidence that polyacrylamide and homopolymeric oligonucleotide were known equivalents for the purpose of providing a spacer linking an oligonucleotide probe to a solid support.

Regarding the length of the polynucleotide spacer, MPEP 2144.05 states regarding the optimization of ranges:

“[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).”

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MPEP 2144.05 also states:

“A particular parameter must first be recognized as a result-effective variable, i.e., a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation. *In re Antonie*, 559 F.2d 618, 195 USPQ 6 (CCPA 1977)”.

Livak teaches: “Hybridization of a probe immobilized to a solid support generally requires that the probe be separated from the solid support by at least 30 atoms, more preferably at least 50 atoms” (column 7, lines 59-62). This statement indicates that separation distance is a result-effective variable for hybridization.

Claims 35, 38, 46, 58 and 84 are rejected under 35 U.S.C. 103(a) as being unpatentable over Guschin et al (1997) as applied to claims 1-8, 11-14, 18, 22, 23, 25-27, 29-34, 39-40, 44-45, 55-57, 59-61, 81, 83 and 87 above, and further in view of Martineau et al (2000).

Guschin teaches all of the limitations of claim 1, upon which claims 35, 38, 46, 58 and 84 depend as discussed in the rejection of claim 1 under 35 U.S.C. 102 above. Guschin does not teach using primers other than the primers capable of amplifying or copying multiple homologous sequences, primers/probes to detect antibiotic resistance, or primers/probes to detect the specific microorganisms recited in claims 35, 38, 46, 58 and 84.

Martineau teaches a method comprising amplifying and detecting antibiotic resistance genes, as well as bacterial 16S rRNA and *Staphylococcus aureus* and *Staphylococcus epidermidis* specific targets in multiplex PCR (see

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figure 1). Martineau uses a primer pair capable of amplifying multiple homologous genes (16S rDNA) from a variety of bacterial species, including *Staphylococcus*, *Enterococcus*, and *Streptococcus* (see figure 1). Martineau does not teach using an array to simultaneously identify the bacterial species and antibiotic resistance by hybridizing the products of the multiplex PCR to an array with oligonucleotide probes covalently bound to a solid support via a spacer of at least 6.8 nm.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention of the instant application was made to combine the multiplex PCR, using primers capable of amplifying 16S rDNA from all bacterial species as well as primers to detect antibiotic resistance genes (as taught by Martineau) with the array method of Guschin in order to achieve simultaneous identification of a bacterial pathogen as well as the antibiotic resistance profile of the pathogen. Further motivation to combine these teachings is provided by Martineau:

“In the clinical setting, the simultaneous identification of the bacteria and determination of its susceptibility to antibiotics generally require 48 h. Yet in the choice of empiric antibiotic therapy for suspected staphylococcal sepsis, the clinician must know rapidly which species is involved and its susceptibility to antibiotics.” (page 237, column 1, last paragraph)

Claim 47 is rejected under 35 U.S.C. 103(a) as being unpatentable over Guschin et al (1997) as applied to claims 1-8, 11-14, 18, 22, 23, 25-27, 29-34, 39-40, 44-45, 55-57, 59-61, 81, 83 and 87 above, and further in view of Gingeras (USPN 6,228,575).

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Guschin teaches all of the limitations of claim 1 upon which claim 47 depends as discussed under the rejection of claim 1 under 35 U.S.C. 102 above. Guschin does not teach identifying Mycobacteria.

However, Gingeras teaches the identification of Mycobacteria is essential for diagnosis and treatment of those infected with HIV (see column 1). Gingeras also teaches Mycobacteria detection is also important for detecting drug resistance (see column 2). Gingeras teaches using arrays comprising Mycobacteria probes (see columns 3, 8-9, 18-23, 28-30 and the examples).

Accordingly, in view of the teachings of Gingeras, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Guschin so as to have identified and/or quantified Mycobacteria. One of ordinary skill in the art would have been motivated to modify the teachings of Guschin in order to have achieved the benefit of providing a valuable means for detecting disease (e.g., tuberculosis, HIV, etc.).

Claim 48 is rejected under 35 U.S.C. 103(a) as being unpatentable over Guschin et al (1997) as applied to claims 1-8, 11-14, 18, 22, 23, 25-27, 29-34, 39-40, 44-45, 55-57, 59-61, 81, 83 and 87 above, and further in view of Boon et al (USPN 6,488,932).

Guschin teaches all of the limitations of claim 1 upon which claim 48 depends as discussed under the rejection of claim 1 under 35 U.S.C. 102 above. Guschin does not teach the sequence to be identified belongs to the MAGE family. However, Boon teaches that is advantageous to detect sequences that

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belong to the MAGE family (which are closely related) for the diagnosis of tumors. See figure 4 and columns 3-8, for example.

Accordingly, in view of the teachings of Boon, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Guschin so as to detect a sequence belonging to the MAGE family. One of ordinary skill in the art would have been motivated to modify the teachings of Guschin in order to have achieved the benefit of providing an effective means of diagnosing a tumor.

Claim 49 is rejected under 35 U.S.C. 103(a) as being unpatentable over Guschin et al (1997) as applied to claims 1-8, 11-14, 18, 22, 23, 25-27, 29-34, 39-40, 44-45, 55-57, 59-61, 81, 83 and 87 above, and further in view of Apple et al (USPN 5,451,512).

Guschin teaches all of the limitations of claim 1 upon which claim 49 depends as discussed under the rejection of claim 1 under 35 U.S.C. 102 above. Guschin does not teach the sequence to be identified belongs to the HLA-A family. However, Apple teaches that is advantageous to detect sequences that belong to the HLA-A family (which are closely related) to help determine potential transplantation donors, thus aiding in minimizing the risk of transplantation rejection. See columns 1-8, for example.

Accordingly, in view of the teachings of Apple, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Guschin so as to detect a sequence belonging to the

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HLA-A family. One of ordinary skill in the art would have been motivated to modify the teachings of Guschin in order to have achieved the benefit of minimizing the risk of transplantation rejection.

Claims 50, 51 and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Guschin et al (1997) as applied to claims 1-8, 11-14, 18, 22, 23, 25-27, 29-34, 39-40, 44-45, 55-57, 59-61, 81, 83 and 87 above, and further in view of Klein et al (USPN 6,255,059).

Guschin teaches all of the limitations of claim 1 upon which claims 50, 51 and 53 depend as discussed under the rejection of claim 1 under 35 U.S.C. 102 above. Guschin does not teach the sequence to be identified belongs to the dopamine or histamine receptors coupled to the G genes family. However, Klein teaches that is advantageous to detect sequences that belong to the dopamine or histamine receptors coupled to the G genes family (which are closely related) to mediate transmembrane signaling by external stimuli, endocrine function, carbohydrate metabolism, etc. See columns 1-4, for example.

Accordingly, in view of the teachings of Klein, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Guschin so as to detect a sequence belonging to the dopamine or histamine receptors coupled to the G genes family. One of ordinary skill in the art would have been motivated to modify the teachings of Guschin in order to have achieved the benefit of mediating transmembrane signaling for many vital biological processes, such as carbohydrate metabolism.



Claim 52 is rejected under 35 U.S.C. 103(a) as being unpatentable over Guschin et al (1997) as applied to claims 1-8, 11-14, 18, 22, 23, 25-27, 29-34, 39-40, 44-45, 55-57, 59-61, 81, 83 and 87 above, and further in view of Murphy et al (WO/9405695).

Guschin teaches all of the limitations of claim 1 upon which claim 52 depends as discussed under the rejection of claim 1 under 35 U.S.C. 102 above. Guschin does not teach the sequence to be identified belongs to the choline receptors coupled to the G genes family. However, Murphy teaches that is advantageous to detect sequences that belong to the choline receptors coupled to the G genes family (which are closely related) for use in diagnosis of neurological, viral or endocrine pathologies. See pages 12-16 and 26-34, for example.

Accordingly, in view of the teachings of Murphy, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Guschin so as to detect a sequence belonging to the choline receptors coupled to the G genes family. One of ordinary skill in the art would have been motivated to modify the teachings of Guschin in order to have achieved the benefit of diagnosing neurological, viral or endocrine pathologies.

Claims 54 and 90 are rejected under 35 U.S.C. 103(a) as being unpatentable over Guschin et al (1997) as applied to claims 1-8, 11-14, 18, 22,

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23, 25-27, 29-34, 39-40, 44-45, 55-57, 59-61, 81, 83 and 87 above, and further in view of Waxman et al (USPN 6,207,648).

Guschin teaches all of the limitations of claim 1 upon which claims 54 and 90 depend as discussed under the rejection of claim 1 under 35 U.S.C. 102 above. Guschin does not teach the sequence to be identified belongs to the cytochrome P450 isoforms family. However, Waxman teaches that is advantageous to detect sequences that belong to the cytochrome P450 isoforms family (e.g., 2D6 and 2C19, which are closely related) for use in treatment of cancer. See columns 3-8, 15-25 and examples).

Accordingly, in view of the teachings of Waxman, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Guschin so as to detect a sequence belonging to the cytochrome P450 isoforms family. One of ordinary skill in the art would have been motivated to modify the teachings of Guschin in order to have achieved the benefit of identifying cytochrome P450 isoforms, which can be used in developing and providing anti-cancer drugs for use in treating cancer.

Claim 86 is rejected under 35 U.S.C. 103(a) as being unpatentable over Guschin et al (1997) as applied to claims 1-8, 11-14, 18, 22, 23, 25-27, 29-34, 39-40, 44-45, 55-57, 59-61, 81, 83 and 87 above, and further in view of Vannuffel et al (WO 99/16780, cited in the IDS).

Guschin teaches all of the limitations of claim 1 upon which claim 86 depends as discussed under the rejection of claim 1 under 35 U.S.C. 102 above.

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Guschin does not teach the sequence to be identified belongs to the *FemA* gene of Staphylococci species. However, Vannuffel teaches the specific detection of Staphylococci species using consensus sequences from the *FemA* *Staphylococcus* nucleotide sequence and *Staphylococcus* species specific probes (see abstract, pages 4-5, 8-13 and examples 1-7). More specifically, Vannuffel teaches a method for identification and/or quantification of staphylococcal species comprising, obtaining a Staphylococcal species from a biological sample, possibly purifying and amplifying said sample, and then identifying said species through hybridization on an oligonucleotide array, wherein the consensus and specific sequences of *FemA* are used as capture nucleotide sequences (pages 11-12). Vannuffel also teaches that the method can be advantageously combined with another specific detection step of possible resistance to antibiotics (page 11). Vannuffel also teaches that the probes of the invention can be immobilized on any solid support suitable for fixation of a nucleic acid (pages. 12-13). Vannuffell teaches that the invention can detect several Staphylococcal species, such as *S. hominis*, *S. saprophyticus*, *S. epidermidis* and *S. haemolyticus* (page 4), and other Gram-positive bacteria (pages 5 and 10).

Accordingly, in view of the teachings of Vannuffel, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Guschin so as to have identified and/or quantified the *femA* sequence of Staphylococcal species. One of ordinary skill in the art would have been motivated to modify the teachings of Guschin in order to have

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achieved the benefit of providing a means of detecting multiple species of the *Staphylococci* genus for use in diagnosing staphylococcal infections.

Claim 89 is rejected under 35 U.S.C. 103(a) as being unpatentable over Guschin et al (1997) as applied to claims 1-8, 11-14, 18, 22, 23, 25-27, 29-34, 39-40, 44-45, 55-57, 59-61, 81, 83 and 87 above, and further in view of Musser (Clin Microbiol Rev. (1995) 8(4): 496-514).

Guschin teaches all of the limitations of claim 1 upon which claim 89 depends as discussed under the rejection of claim 1 under 35 U.S.C. 102 above. Guschin does not teach the sequence to be identified belongs to a gene encoding sub-unit of A gyrase. However, Musser teaches that is advantageous to detect sequences that belong to the gene encoding gyrase A for use in determining antimicrobial agent resistance (see pages 506-507).

Accordingly, in view of the teachings of Musser, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Guschin so as to detect a gene encoding gyrase A. One of ordinary skill in the art would have been motivated to modify the teachings of Guschin in order to have achieved the benefit of determining antimicrobial agent resistance.

Claims 91 and 93 are rejected under 35 U.S.C. 103(a) as being unpatentable over Guschin et al (1997) as applied to claims 1-8, 11-14, 18, 22,

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23, 25-27, 29-34, 39-40, 44-45, 55-57, 59-61, 81, 83 and 87 above, and further in view of Rose et al (Nuc. Acid Res. (1998) 26(7): 1628-1635).

Guschin teaches all of the limitations of claim 1 upon which claims 91 and 93 depend as discussed under the rejection of claim 1 under 35 U.S.C. 102 above. Guschin does not teach the sequence to be identified belongs to animal species such as Galinaceae or plant species of barley. However, Rose teaches the amplification of distantly related sequences including chicken and barley by using consensus primers (see abstract and pages 1629-1634). Rose teaches this method is advantageous for isolating sequences of distantly related (e.g., homologous) sequences (see pages 1628-1629 and 1635).

Accordingly, in view of the teachings of Rose, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Guschin so as to detect animal species such as Galinaceae or plant species of barley. One of ordinary skill in the art would have been motivated to modify the teachings of Guschin in order to have achieved the benefit of determining distantly related sequences such as chicken and barley.

Claim 92 is rejected under 35 U.S.C. 103(a) as being unpatentable over Guschin et al (1997) as applied to claims 1-8, 11-14, 18, 22, 23, 25-27, 29-34, 39-40, 44-45, 55-57, 59-61, 81, 83 and 87 above, and further in view of Apostolidis et al (Heredity (1996) 77(6): 608-618, abstract only).

Guschin teaches all of the limitations of claim 1 upon which claim 92 depends as discussed under the rejection of claim 1 under 35 U.S.C. 102 above.

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Guschin does not teach the sequence to be identified belongs to fish species such as *S. trutta*. However, Apostolidis teaches the genetic differentiation and phylogenetic relationships among Greek *S. trutta* populations as revealed by PCR (see abstract). Apostolidis teaches this method is advantageous for differentiating different trout species in various populations (see abstract).

Accordingly, in view of the teachings of Apostolidis, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Guschin so as to detect fish species such as *S. trutta*. One of ordinary skill in the art would have been motivated to modify the teachings of Guschin in order to have achieved the benefit of differentiating different trout species in various populations.

Claim 94 is rejected under 35 U.S.C. 103(a) as being unpatentable over Guschin et al (1997) as applied to claims 1-8, 11-14, 18, 22, 23, 25-27, 29-34, 39-40, 44-45, 55-57, 59-61, 81, 83 and 87 above, and further in view of Dickinson et al (Pub. No. US 2002/0102578).

Guschin teaches all of the limitations of claim 1 upon which claim 94 depends as discussed under the rejection of claim 1 under 35 U.S.C. 102 above. Guschin does not teach the sequence to be identified genetically modified organisms. However, Dickinson teaches the use of probe arrays comprising GMOs, which can be used for checking seed lots, only the intended strains are present, and to validate that the product is GMO free (see pages 34-35).

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Accordingly, in view of the teachings of Dickinson, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Guschin so as to detect GMOs. One of ordinary skill in the art would have been motivated to modify the teachings of Guschin in order to have achieved the benefit of ensuring a product is the intended product, and that the product is GMO free, if desired.

### ***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-8, 11-18, 20-23, 25-27, 29-36, 38-40, 44-61, 81, and 83-94 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2, 4, 9-10, 12-23, 38, 40, 42, 44-

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45 of copending Application No. 09/817014. Although the conflicting claims are not identical, they are not patentably distinct from each other because the only differences in the limitations of the independent claims (claim 1 in both applications) is the added limitation in claim 1 of the '014 application that the homologous sequences to be amplified share more than 60% homology, and the the spacer comprises a nucleotide sequence of at least 40 bases. Thus claim 1 of the '014 application represents a species of the more generic claim 1 of the instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1-8, 11-18, 20-23, 25-27, 29-36, 38-40, 44-61, 81, and 83-94 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3, 5-10, 13, 16-17, 19-25 of copending Application No. 10/111748. Although the conflicting claims are not identical, they are not patentably distinct from each other because the only differences in the limitations of the independent claims (claim 1 in both applications) is the added limitation in claim 1 of the '748 application that the homologous sequences to be amplified share more than 60% homology, specific primer sets for amplification are required, and no spacer is required to link the capture oligonucleotides to the solid support. Thus claim 1 of the '748 application represents a species of the more generic claim 1 of the instant application.



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This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1-8, 11-18, 20-23, 25-27, 29-36, 38-40, 44-61, 81, and 83-94 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-28 of copending Application No. 10/860388. Although the conflicting claims are not identical, they are not patentably distinct from each other because the only differences in the limitations of the independent claims (claim 1 in both applications) is the added limitation in claim 1 of the '388 application that the homologous sequences to be amplified share more than 85% homology, and at least 2 sets of primer pairs are required to be used. Thus claim 1 of the '388 application represents a species of the more generic claim 1 of the instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

### ***Conclusion***

No claims are allowed.

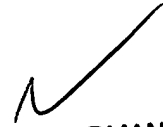
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Woolwine whose telephone number is (571) 272-1144. The examiner can normally be reached on Mon-Fri 9:00am-5:00pm.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

scw



JEFFREY FREDMAN  
PRIMARY EXAMINER

2/10/06